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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/842,234	04/26/2001	Kiyoshi Nakayama	P20938	7436

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EXAMINER
RAO, DEEPAK R

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/25/2002 11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/842,234	Nakayama et al.
Examiner	**Art Unit**
Deepak Rao	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 13, 2002*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *1-3 and 5* is/are allowed.

6) ☒ Claim(s) *4, 6, 7, 12-23, 26, and 27* is/are rejected.

7) ☒ Claim(s) *8-11, 24, and 25* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This office action is in response to the amendment filed on August 13, 2002.

Claims 1-27 are pending in this application.

The following rejections are withdrawn:

The rejection under 35 U.S.C. 112, second paragraph is withdrawn in view of the amendment.

The rejection under 35 U.S.C. 102(b) over Nishigaki et al. (Chem. Pharm. Bull. 1975) is withdrawn in view of the amendment.

Claim objection under 37 CFR 1.75 is withdrawn in view of the amendment and applicant's remarks that 'applicant can express the invention in a reasonable number of ways'.

The following rejections are maintained:

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for therapeutic treatment of microbial infection when the compound is used together with an antimicrobial agent, does not reasonably provide enablement for the "preventive treatment" of the microbial infection, etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons of the previous office action are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant argues that the instant compounds have 'inhibitory action against drug efflux pumps of microorganisms', which action in turn 'prevents the formation of infection'. This is not found to be persuasive because based on the explanation provided by the applicant, microorganism or infection due to bacterium must be present in order for the compounds to be effective. The compounds are established as drug efflux pump inhibitors which means that the compounds act on the bacterium by blocking the drug defluxing activity of the microorganism. This establishes the use of the compounds in 'combination therapy' (i.e., combined with other antimicrobial agent) of the microbial infection because the compounds are not protecting the subject from acquiring infection due to bacterium, but acting on the preexisting microorganism. Applicant also clearly submits that "the presently claimed invention can act on a bacterium" (see page 14, lines 16-17) thereby providing that the compounds are not acting on a sterile or non-infected subject.

The specification does not provide any enablement for the "preventive treatment" action by which the instantly claimed compounds 'prevent' the subject from bacterial infection. Applicant also submits that the instant compounds being drug efflux pump inhibitors, 'enhance the antibacterial action of an antibacterial agent' (see page 14, lines 17+) which raises further question regarding the antibacterial activity of the claimed compounds. Test examples 1-3 provided in the specification are towards the 'effect of combined use with antimicrobial agent' and there are no test examples that provide the antimicrobial action of the claimed compounds.

There is nothing on record that provides 'preventive' activity for the instantly claimed compounds or other antibacterial agents. It is emphasized in the specification and the arguments that the instant compounds are enhancers of antibacterial action of other antibacterial agents, however the specification does not provide any enablement for the 'preventive' activity of the compounds against infection due to microorganism. For all the above reasons, it is maintained that the specification fails to establish the use of the compounds in "preventive treatment" of the microbial infection.

The following rejections are under new grounds and/or necessitated by the amendment:

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-7, 12-18, 20-23, 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for therapeutic treatment of microbial infection when the compound is used together with an antimicrobial agent, does not reasonably provide enablement for the "preventive treatment" of the microbial infection or the "therapeutic treatment" of the microbial infection when the compound is administered without an antibacterial agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The reasons provided in the previous office action including the discussion of the *In re Wands* factors and the arguments above are incorporated here by reference with respect to "preventive treatment" using the compounds alone or together with an antimicrobial agent.

The instant claims are drawn in part to 'a medicament composition for therapeutic treatment of microbial infection' or 'a method of therapeutic treatment of a microbial infection' using the compound of formula (I) as an active ingredient, for which the specification does not provide any enablement. The specification provides that 'the medicament according to the instant invention acts on a microorganism with acquired resistance to an anti microbial agent, and eliminates the resistance of the bacteria by inhibiting a drug efflux pump to improve the effect of antimicrobial agent', see page 2, lines 24-27. The specification does not provide that the compounds of the invention act as antimicrobial agents. Further, the test examples 1-3 provided at pages 169-177 are all drawn to the 'effect of combined use of the instant compound with an antimicrobial agent' which establish the use of the compounds as drug efflux pump inhibitors in enhancing the activity of an antimicrobial agent used in the combination therapy. The specification does not provide any test data showing that the instant compounds individually possess antimicrobial activity and therefore, are useful as active ingredient effective against microbial infection in a medicament composition or a method of use when used without the presence of an antimicrobial agent.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the

instant method claims. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19, 21, 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nishigaki et al. (Chem. Pharm. Bull. 1975). The reference teaches certain 1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid compounds, see the formula Table I, page 3172 that are useful as antibacterial agents and the species of Compound No. 45. The instant claims differ by reciting R^{14} to be an alkyl group having 1, 3 or 4 carbon atoms whereby the instant compounds differ from the reference compound by a $-CH_2$ group (when R^{14} is alkyl having 1 or 3 carbon atoms) and thus, the instant compounds are homologs of the reference compounds. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally similar compounds are expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are prima facie obvious, absent a showing of unexpected results. *In re Hass*, 60 USPQ 544 (CCPA 1944); *In re Henze*, 85 USPQ 261 (CCPA 1950).

Allowable Subject Matter

Claims 1-3 and 5 are allowed. The references of record, for example, Nishigaki et al., do not teach or fairly suggest the instantly claimed compounds.

Claims 8-11 and 24-25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Receipt is acknowledged of the Information Disclosure Statement filed on September 26, 2002 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (703) 305-1879. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Deepak Rao
Primary Examiner
Art Unit 1624

November 22, 2002